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Microbicides: New Potential for Protection

What are microbicides?

Microbicides are substances that are designed, when applied vaginally, to reduce transmission of HIV or other sexually transmitted infections (STIs). Some microbicides under development also function as spermicides to provide contraceptive protection. Eventually, microbicides are likely to be available as gels, creams, films, suppositories, or vaginal rings.



KEY POINTS

- **Scientists currently are studying over 60 substances as possible microbicides.**

Some 45 of these substances are in laboratory or animal testing, and 17 are in various stages of human testing. Five are in or about to enter phase III clinical trials—the final stage of testing—which will determine how well these microbicide candidates prevent HIV infection and how safe they are for long-term use. If safety and effectiveness are established in clinical trials, a microbicide could be marketed perhaps as early as 2010 (26).

- **Effectiveness remains uncertain.** It is not yet known whether any of the five microbicides in phase III clinical trials will prove able to protect against HIV at all. If so, it may only be 50–60% effective in preventing HIV and other STIs, providing substantially less protection than condoms when used consistently and correctly. But future generations of microbicides are likely to be more effective than the first generation, less costly, and better able to meet people's needs (106).

- **Microbicides could save millions of lives.** A vaginal microbicide that is used more consistently than condoms might prevent more HIV and STI infections than condoms do in actual use. Many sexually active people are at risk for HIV/AIDS because they do not use condoms or do not use them consistently and correctly, while people probably would be more likely to use microbicides than condoms. One estimate is that 2.5 million lives would be saved in the first three years after microbicides are introduced (28, 97).

- **Women could control microbicide use.** One advantage of microbicides over condoms is that women could use them without their partners' cooperation. Microbicides would offer women, who often lack the power to control sexual activity or condom use, a method to reduce their vulnerability.

- **Public interest could be substantial.** Many women and men would have great interest in using microbicides, studies show. People differ widely, however, in the characteristics of the ideal microbicide they would prefer—a fact suggesting that manufacturers should provide a wide range of choices.

- **Introduction strategy is crucial to access.** For microbicides to fulfill their promise, they must be accessible and affordable. A successful introduction strategy would involve manufacturers, suppliers, public health systems, and governments and would include communication, marketing, logistics, and pricing plans.

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Five Microbicides in Final Stages of Testing

Microbicides, like drugs and medical devices, must go through several stages of rigorous testing for safety and effectiveness in order to obtain approval from regulatory agencies such as the US Food and Drug Administration (US FDA). The first stages focus on safety of use and product acceptability. The final stage focuses on effectiveness—that is, the ability of a microbicide in typical use to reduce the average rates of infections when compared with control groups, as well as long-term safety and acceptability (11) (see Table 1).

If successful, one or more of the five products entering phase III clinical trials is likely to reach the market. These five products are: *BufferGel*[®], *Carraguard*[®], *PRO 2000*[®], C31G, and cellulose sulfate (2, 44) (see Table 2).

A sixth product, dextrin-2-sulfate (*Emmelle*[®]), was poised to enter phase III clinical trials in 2005, but the organization running the trial, the UK Medical Research Council's Microbicides Development Programme (MDP), pulled it from the clinical trial. In a statement the organization explained that three other products of a similar type were already entering phase III clinical trials, and dextrin-2-sulfate did not prove as effective as the others in preclinical tests (78).

Most microbicides under development, including the five in phase III clinical trials, act in one or more of the following ways (44):

1. Vaginal defense enhancers boost the body's natural defenses against infection by increasing lactobacilli or by rapidly acidifying the ejaculate, reinforcing the natural mild acidity of the vagina that inactivates both sperm and STIs. *BufferGel* is a vaginal defense enhancer.

2. Surfactants damage the surface membranes of disease pathogens, thereby disabling them and preventing them from causing infection. C31G is a surfactant.

3. Entry and fusion inhibitors bind to disease pathogens or to healthy cells before pathogens have a chance to invade and attach to them. *Carraguard*, *PRO 2000*, and cellulose sulfate are entry and fusion inhibitors.

4. Replication inhibitors prevent viruses from replicating in cells that they have entered. Replication inhibitors are still in preclinical studies or in phase I or phase II clinical trials. None has yet reached phase III.

Vaginal defense enhancers boost natural defenses against diseases. The vagina is normally too acidic for sperm to survive. During sexual intercourse

semen, which is alkaline, neutralizes the acidity of the vagina, making it more likely that sperm—and also HIV and other pathogens—will survive. Acid-buffering microbicides make the semen acidic, which keeps the vagina acidic, thus inactivating sperm and several STI organisms, including HIV (65, 86).

BufferGel (carbomer 974P)¹, developed at Johns Hopkins University and ReProtect, Inc., a biotechnology firm, reinforces

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¹ Some microbicide candidates are typically known by their brand name, such as *BufferGel*, while others are known by their chemical agent, such as C31G. In this section each microbicide is introduced by the name most commonly used, followed by its other name, whether product or chemical, in parentheses. Thereafter, throughout the text the product is referred to by the name most commonly used. Product names are in italics, while chemicals are in roman type.

TABLE 1 Clinical Trial Phases Applicable to Microbicides

Phase	Number of Participants	Length of Treatment and Follow-up	Objectives
Phase I	10–100	1 to 2 weeks	To assess local and systemic safety and acceptability and to determine dose and formulation. May run into a phase II trial (called phase I/II).
Phase II	50–200	2 to 6 months	To assess safety and acceptability over a longer time.
Phase II/IIb	50–500	6 months to 2 years	To screen for products reaching a minimum level of effectiveness. Smaller, less costly than phase III, but numbers of participants and length of follow-up indicate whether a subsequent larger trial would be worthwhile. If so, participants continue from one trial to the next, and additional participants are recruited (called phase II/III).
Phase III	1,000–30,000	1 to 2 years	To evaluate effectiveness in preventing HIV infection and other STIs and to assess long-term safety and acceptability. Some phase III trials will involve multiple products, which will require more participants than those testing only one product.

Note: Phases I/II, II/IIb, and II/III are variants of study designs or studies that move from one clinical trial phase to the next. Number of participants and length of treatment and follow-up vary. Sources: Adapted from Stone, 2003 (112), Fleming, 2004 (27), Mauck et al., 2001 (71), and the Alliance for Microbicide Development, 2004 (3).

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the protective vaginal acidity to kill sperm, microbes that cause some STIs, and also white blood cells infected with HIV (86, 127). Clinical trials provide some evidence that *BufferGel* also treats bacterial vaginosis, a condition

that increases the risk of HIV infection (46, 122).

Clinical trials in India, Malawi, Thailand, Zimbabwe, and the US have found that *BufferGel* is non-toxic, and rates of vaginal irritation were similar to those in an earlier

study of women using no vaginal product (76). In a US clinical trial most of the 48 men who completely coated the penis with *BufferGel* for seven consecutive nights found it acceptable and reported they would use it and not object to their

TABLE 2 Microbicides Entering Phase III Clinical Trials

Mechanism of Action	Microbicide Name	Description	Potential Pregnancy Prevention?	Potential STI/HIV Protection*
Vaginal defense enhancer	<i>BufferGel</i> (carbomer 974P)	Polymer gel reinforces vaginal acidity by acidifying the ejaculate.	Yes	HIV, chlamydia, herpes, HPV
Surfactant	<i>C31G (Savvy)</i>	Detergent disrupts viral, bacterial, and cell membranes, including those of sperm.	Yes	HIV, chlamydia, herpes
Entry and fusion inhibitor	<i>Carraguard (PC-515)</i>	Carrageenan (derived from seaweed) binds to viruses to block them from attaching to and infecting healthy cells.	No	Herpes, HPV, gonorrhea
	<i>PRO 2000</i> (polynaphthalene sulfonate)	Binds to viruses and bacteria to prevent them from attaching to and infecting healthy cells.	Yes	HIV, gonorrhea, herpes
	<i>Cellulose sulfate (Ushercell)</i>	Binds to viruses and bacteria to prevent them from attaching to and infecting healthy cells.	Yes	Gonorrhea

* As demonstrated in animal models
HIV = human immunodeficiency virus

HPV = human papillomavirus
Source for potential STI/HIV protection: Zeitlin, 2002 (128)

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partners' use. Side effects were not significantly different from those of a placebo (114).

A phase II/III study of *BufferGel* is currently evaluating the contraceptive effectiveness of the substance when used with a diaphragm. A phase II/IIIb HIV-prevention clinical trial will begin in late 2004 in India, Malawi, South Africa, Tanzania, the US, Zambia, and Zimbabwe to evaluate the safety and effectiveness of *BufferGel* and *PRO 2000* in over 3,000 women (see p. 5, middle column). The US National Institute of Allergy and Infectious Diseases (NIAID) and the HIV Prevention Trials Network (HPTN) are sponsoring this clinical trial (17).

Surfactants disable bacteria and viruses. Surfactants (also known as detergents) kill or disable bacteria or viruses by damaging bacterial membranes and viral envelopes (surface membranes). In this they are similar to currently available spermicides that act as surfactants, such as nonoxynol-9 (N-9) (94). Hundreds of chemicals can kill HIV, but researchers are looking for a surfactant that will not disrupt epithelial cells (the thin, protective layer of cells lining the vagina) and that has few side effects (119).

N-9 has been used for decades, before HIV appeared, as a spermicide in contraceptive foams and gels and to lubricate condoms. In lab tests N-9 rapidly and potently inactivates HIV and other STIs as

well as killing sperm (25, 64, 113). Therefore, researchers had hoped that N-9 would prove to be an effective microbicide (57). Recent research, however, has found that N-9 can disrupt epithelial cells in the vagina among women who have sex several times a day, thereby increasing the risk of HIV infection (61, 101, 102, 120, 123).

In 2003 the World Health Organization (WHO) recommended that people not use N-9 for protection against HIV/AIDS or other STIs (126). There is some concern that candidate microbicides that work as detergents may have effects similar to those of N-9 on the epithelial cells in the vagina. Extended safety tests would help determine whether or not they cause similar problems (19).

C31G (*Savvy*®) is a microbicide developed by Biosyn, Inc. C31G is a surfactant that diffuses through cervical mucus more rapidly than N-9 and, at low concentrations, is not as toxic to vaginal cells (60). In laboratory tests C31G kills sperm cells and also kills a variety of STI pathogens, including HIV (69, 124). It does not work, however, against viruses such as human papillomavirus (HPV) that are not encased in a membrane (124).

The nonprofit research organization CONRAD, in several phase I and phase I/II clinical trials among men and women using C31G, has found that the substance is well tolerated at low doses after 3 to 14 continuous days of use (69, 74, 75). In a phase I clinical trial among women who applied C31G before sex, it significantly reduced the number of motile sperm in the vagina after sex (73).

Phase III clinical trials have begun in Ghana among more than 2,200 women to test effectiveness of C31G against HIV, and another phase III clinical trial has begun in Nigeria. Results from both studies are expected by 2007. Family Health International (FHI) is conducting these clinical trials, with funding from the US Agency for International Development (USAID) (9, 33). Additionally, a phase III clinical trial to test contraceptive effectiveness has begun in the US in over 1,000 women, funded by the US National Institute of Child Health and Human Development (21).

Entry and fusion inhibitors block pathogens. Entry and fusion inhibitors, including *Carraguard*, *PRO 2000*, and cellulose sulfate, bind to pathogens, thus preventing them from attaching to host cells, or they bind to potential host target cells, forming a protective coating that prevents pathogens from attaching. Many of these products are nonspecific blockers—that is, they act against multiple organisms, including microbes that cause HIV and other STIs (44).

Carraguard (PC-515), being developed by the Population Council, is a microbicidal gel containing carrageenan, a sulfated polysaccharide derived from seaweed. Researchers suspect that *Carraguard* binds to viruses, including HIV, HPV, and herpes simplex virus (HSV), thereby blocking them from sticking to healthy cells (88). *Carraguard* appears not to be spermicidal, however.

Carraguard is inexpensive to make (93). Another advantage is

that, because carrageenan is commonly used in cosmetics, toothpastes, and food, it is expected to be safe and nontoxic when used as a microbicide. In clinical trials *Carraguard* is distributed in prefilled, single-dose, disposable plastic applicators. Users press a small bulb between the thumb and forefinger to squeeze out the contents of the applicator into the vagina through the elongated nozzle (93).

Preliminary data from a phase I clinical trial in Thailand found that men who applied *Carraguard* before sex over three months did not experience significantly more irritation than a control group of men using a placebo (59). Phase II studies among 400 HIV-negative healthy women in South Africa and among 165 such women in Thailand confirmed topical safety (that is, safety to the vaginal epithelium) (92). A phase III trial to determine the effectiveness of *Carraguard* in preventing HIV transmission among 6,270 women in South Africa began in March 2004 and is expected to continue for at least three years (92).

PRO 2000 (polynaphthalene sulphonate), produced by Indevus

Pharmaceuticals in the US, binds to HIV and other STI pathogens, preventing them from infecting human cells. Phase I clinical trials in Belgium, South Africa, the UK, and the US have demonstrated the topical safety and acceptability of *PRO 2000* in low doses, although one-third to two-thirds of women experienced mild vulval irritation or leaking of the microbicide from the vagina (77, 121). A phase I trial among 97 men found that side effects of *PRO 2000* were not significantly different from those of a placebo (114). The developer may produce formulations to prevent pregnancy as well as STIs (2, 96).

A phase II/IIb HIV-prevention clinical trial involving 3,100 women in seven countries is starting in late 2004, sponsored by HPTN, to evaluate the safety and effectiveness of a low-dose of *PRO 2000* and *BufferGel*. In addition, the MDP is planning a phase III clinical trial to begin in 2005 in Cameroon, South Africa, Tanzania, Uganda, and Zambia to test high and low doses of *PRO 2000* in 12,000 women (79, 100).

Cellulose sulfate (*Ushercell*TM), developed by Polydex Pharmaceuticals Ltd. in Canada, has been

undergoing evaluation since the early 1990s. In laboratory and animal studies it acts against a broad range of STIs (5, 72). It also appears to have a contraceptive effect (4).

Several phase I clinical trials conducted by the Global Microbicide Project, HPTN, and WHO have demonstrated that cellulose sulfate is safe and less irritating than N-9 (72) for both women and men (70). Another phase I trial in Cameroon found that, when cellulose sulfate was compared with a nonmicrobicidal gel (*KY Jelly*[®]), there was no difference in the rates of epithelial disruption, candidiasis (yeast infection), or bacterial vaginosis or in the acceptability of the two products (20). Researchers have completed additional safety studies with similar results in India, Nigeria, and Uganda (66) and also in the US (105).

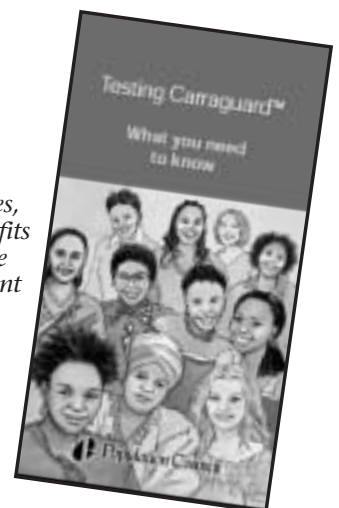
Researchers are planning phase III clinical trials to assess the effectiveness of cellulose sulfate. These trials are expected to begin in late 2004 or early 2005, involving over 2,500 women in Benin, Burkina Faso, India, Kenya, Nigeria, South Africa, and Uganda. CONRAD and FHI are conducting these studies (91, 118).

Research Process Prolonged

Researchers have been pursuing the development of microbicides for almost 20 years (13). Until recently, microbicide development progressed slowly, in part because resources for research and development were scarce, including funding, expert researchers, and a research infrastructure (110, 111).

Clinical trials in particular face additional obstacles (18, 35). To reduce risk of HIV infection among participants in clinical trials, researchers encourage all participants to use condoms. This is an important precaution because some participants will receive a microbicide that has yet to be proven effective, while others will

A booklet from the Population Council about study procedures, risks, and benefits helps to achieve informed consent in a phase III clinical trial.





receive a placebo—containing no microbicide at all. In some clinical trials, still other participants will receive only condoms. Because some people in all groups will use condoms, HIV transmission rates will be lower than they otherwise would be. Thus more participants and a longer study period will be required to detect a difference in HIV transmission rates between groups—the objective of the studies. Researchers often find it challenging to recruit enough volunteers to provide significant results (71, 99, 110).

The funding for clinical trials is

often insufficient to support the large participation necessary, and the number of feasible sites for clinical trials is limited (13, 109). Disagreements among researchers related to the design of clinical trials and protocol have contributed to delays (18, 27, 35).

The regulatory process is lengthy. In many developing countries approval of medical products is heavily influenced by the decisions of the US FDA and European Medicines Evaluation Agency (EMA) (18, 80). Regulatory authorities in developed countries, however, are likely to take a more conservative approach to regulatory decisions about microbicides than are those in most developing countries (18, 27).

Although both developing and developed countries require demonstration of safety and effectiveness before a medical product can be marketed, regulatory processes in developed countries may take longer than some developing countries are prepared to wait (18). The need for a microbicide is especially urgent in developing countries where HIV/AIDS is at catastrophic levels. To hasten microbicide introduction, some microbicide advocates recommend that the regulatory agencies of some developing countries, such as South Africa and India, evaluate the results of candidate microbicide clinical trials independently, rather than wait for the US FDA and EMA to complete their review processes (95, 108).

Microbicides To Join Condoms in Saving Lives

The first generation of microbicides to reach the market will probably not be as effective as male condoms in protecting against STIs, including HIV/AIDS, when each method is used consistently and correctly (106). Male condoms are 90–95% effective in preventing HIV when used consistently and correctly (90). In contrast, the first microbicides are expected to be just 50–60% effective with consistent and correct use (110).

Many people do not use condoms, however, or use them incorrectly and inconsistently (32). In actual use, therefore, a vaginal microbicide might prevent more HIV and STI infections than con-

doms do in typical use, if more people use microbicides and use them correctly (28, 58, 97).

Microbicides, even though they are less effective than condoms, would prevent more infections than condoms now prevent because higher rates of use would more than make up for lower effectiveness rates. For instance, if microbicides are 50% effective, then high-risk groups using them in half of their sex acts would have about the same level of protection against HIV as people who use condoms only in one-quarter of their sex acts, even assuming that condoms are 95% effective (28).

The public health benefits of even a partially effective microbi-

cide would be substantial. One conservative estimate based on computer modeling is that, even if only 20% of people in high-risk groups used a microbicide that was just 60% effective in protecting against HIV infection, 2.5 million lives would be saved in its first three years (97).

Widespread availability of microbicides could reduce condom use somewhat, as some people switch from condoms to microbicides for protection (58, 97). Nevertheless, computer modeling demonstrates that shifts from condom use to microbicide use would rarely be enough to result in an increase in HIV infection rates (28, 58).

Second- and third-generation microbicides are likely to be more effective than the first-generation formulas (106). They will combine several active ingredients in a formulation that works in several ways to combat infection. These advances would decrease the potential for pathogens to develop resistance to the microbicide, protect people who are HIV-positive from reinfection, and protect against more STIs. They would reduce the concentration of potentially toxic agents, reducing irrita-

tion to the vaginal epithelium and toxicity to the natural, beneficial organisms in the vagina (106).

For example, preliminary studies of *PRO 2000* and a monoclonal antibody (a type of vaginal defense enhancer) have found that, when used together, they could provide better protection than the sum of the protection that each affords individually (29). Also, researchers at the Population Council are working on developing PC-815, which is a combination of *Carraguard*,

an entry and fusion inhibitor, and MIV-150, a replication inhibitor (103).

Widespread acceptance and use of microbicides could lead to considerable savings in public health expenditures. Computer modeling projects a savings over three years of US\$2.7 billion worldwide in health-system costs and an additional US\$1 billion in productivity savings because of less worker absenteeism and lower employee training and replacement costs related to STIs (97).

Women Could Control Microbicide Use

Microbicides could help women protect themselves against STIs when they cannot use condoms. Women could control use of microbicides, perhaps without needing the cooperation of their partners.

Some women lack the power to ensure consistent and correct condom use. Relationships that subject women to coercion, violence, and dependency can make it difficult or impossible for them to negotiate condom use or to leave the relationship even though it puts their health at risk (10, 50, 54). While microbicides will not level these power imbalances, they could give women another option to reduce their vulnerability to STIs, including HIV/AIDS (99, 125).

Some women may not be able to use a microbicide without detection by their partners. Consequently, some women facing risk of violence from their partners may not be able to use a microbicide (67). For those not at risk of violence, however, dis-

cussing microbicide use with their partners could help increase intimacy and shared responsibility for HIV protection (68).

Women who lack the power to ensure the use of condoms are at far greater risk than men because women are biologically more vulnerable to HIV and its consequences. The rate of transmission of HIV from men to women is at least two to eight times greater than the rate of transmission from women to men because during sex the vaginal epithelium is easily torn and there is more HIV in semen than in vaginal secretions (24, 84, 87). Adolescent women are at greatest risk because the cervix is physiologically less mature and therefore more vulnerable to infection (104).

Some of the microbicides currently under development would provide women a method to protect themselves not only against HIV/AIDS and other STIs but also



Women pose outside a teaching hospital in Soweto, South Africa. Researchers at the hospital are assessing the prevalence of HIV and whether a microbicides clinical trial in Soweto would be feasible.

against pregnancy—that is, they would provide dual protection. Conversely, some microbicides may allow women to become pregnant while reducing the risk of HIV or other STI transmission, which is not possible with condoms, which protect against both STIs and pregnancy when used consistently and correctly. In cultures where a woman's status and self-esteem depend primarily on her fertility, many women will want the ability to become pregnant but at the same time to reduce their risk of HIV/AIDS (85).

Investment and Funding Are Crucial

Several organizations advocating microbicides have estimated the costs of microbicide development, based on average costs of phase I, II, and III clinical trials and average registration costs—that is, the costs involved in obtaining regulatory approval in a country. The Rockefeller Foundation’s Microbicide Initiative in 2002 estimated that developing a single microbicide from preclinical research to registration would cost an average of \$US57 million (89). Another estimate from the same study was that about US\$775 million in direct product development costs would be required over five

years to complete clinical trials for all of the microbicides then in the development pipeline.

A more recent estimate by the Alliance for Microbicide Development, based on new expenditure data from developers, estimated the cost for developing a microbicide candidate at approximately US\$35 million. The total cost of moving the most advanced products through the final stages of research and to market was estimated to be US\$966 million or more for the 12-year period 2004–2016 (63).

The costs could prove to be substantially lower or higher than these estimates. The development

costs of each microbicide product differ widely and depend on many factors—for example, whether the compound is new or has been used previously, and whether it requires long-term studies of toxicity or carcinogenicity (30). For these reasons new estimates will be made in 2005, based on an extensive review of the costs of all products in development (42).

One estimate puts government funding and private grants for microbicide development for the four-year period 2001 to 2005 at about US\$230 million worldwide (89). The Alliance for Microbicide Development estimates government funding and private grants

for 2001–2004 to be substantially higher, at US\$487 million (42). Still, these estimates are much lower than the funds needed to develop a microbicide candidate.

Current clinical trials in 19 countries (15 developing and 4 developed) are supported almost exclusively by small biotechnology companies, academic centers, nonprofit and government organizations, and private foundations (43). (See “Key Organizations Supporting Microbicide Development,” p. 13.)

Microbicide Clinical Trial Sites



Microbicide clinical trials are underway in 19 countries—15 developing and 4 developed.

Advances in microbicide development have come almost exclusively through public-sector investment (53, 94). The US and British governments (47, 116) and the European Commission (55) have contributed substantially. Such private US organizations as the Rockefeller Foundation, the American Foundation for AIDS Research (amfAR), and the Hewlett Foundation also have funded microbicide development and clinical trials in recent years. The Bill and Melinda Gates Foundation alone has provided US\$124 million as of 2004 (107).

No major pharmaceutical company has made a substantial contribution to microbicide development

(43, 128). Major pharmaceutical companies have been reluctant to invest heavily in microbicide research and development because of liability concerns, regulatory hurdles, high costs, disinterest in non-prescription products, and an uncertain market for microbicides (48, 56, 89). These companies are likely to become interested in microbicide research, however, if a first-generation microbicide produces a high level of demand (81).

Initially, as the developers introduce the first generation of microbicides, the expected potential world market for them is estimated at about US\$1 billion per year. Over the long term, as microbicide formulations

improve, this figure could grow to between US\$1.8 billion and US\$2.6 billion per year (89).

Bringing an effective microbicide to market soon will require close collaboration among public and private research institutions and the major pharmaceutical companies (31, 56). Governments can further encourage private firms to develop microbicides by lowering the costs and risks of research and development. For example, governments can offer tax credits, make it easier for researchers to conduct clinical trials, and conduct regulatory reviews faster to support companies that conduct microbicide research and development (1).

Studies Suggest Substantial Interest

Many women and men would have great interest in using microbicides, acceptability studies indicate (7, 14, 15, 23). Acceptability studies ask people what characteristics they would prefer in such a product and whether they would be likely to use a microbicide (67).

Of the 61 microbicide acceptability studies done between 1995 and 2002, 24 focused on developed countries, 25 on countries in sub-Saharan Africa, 6 in Asia, and 1 in Latin America, while 5 covered multiple regions. Most acceptability studies are among people who have not used a microbicide because formulations appropriate for testing have only recently become available.

Nevertheless, more than one-

quarter (17 of the 61) are among people using candidate products in clinical trials for up to 14 days. Clinical trials provide the best information on acceptability because study participants can report their detailed experiences with using an actual product (67).

People's interest in using a microbicide appears likely to depend on the level of severity of the AIDS epidemic in an area. Where HIV/AIDS is widespread, acceptability studies find that women perceive their risk to be high, and interest in microbicides is substantially greater than where HIV/AIDS is less prevalent (6, 83).

What formulations would people prefer? To guide microbicide development, researchers

have conducted detailed studies on what people would prefer as to formulation, degree of protection, applicator, packaging, color, and other characteristics (38). For instance, an acceptability study among 635 Brazilian women of various ages and backgrounds suggests that an ideal microbicide would be odorless, colorless, a cream rather than a suppository, placed in the vagina with an applicator rather than with the fingers, applied well before sex rather than just beforehand, and protective against all STIs, not just HIV.

In this study 96% of respondents said they would use a microbicide if they could apply it only with an applicator, while 76% said they would use it even if they had

to insert a finger to apply it. Yet in interviews most respondents expressed discomfort with either inserting an applicator or touching their vaginas. Such findings suggest that manufacturers, distributors, and reproductive health programs probably would need to help women feel comfortable touching themselves in order to assure widespread acceptance and long-term, effective use of microbicides (37).

Over 99% of respondents in the Brazilian study said that they would prefer a formulation if it offered dual protection against STIs and pregnancy. Also, a majority would want microbicidal effects to last at least eight hours. The researchers concluded that women's interest in a formulation that could be used well before intercourse indicates a desire to maintain privacy or intimacy (39, 40).

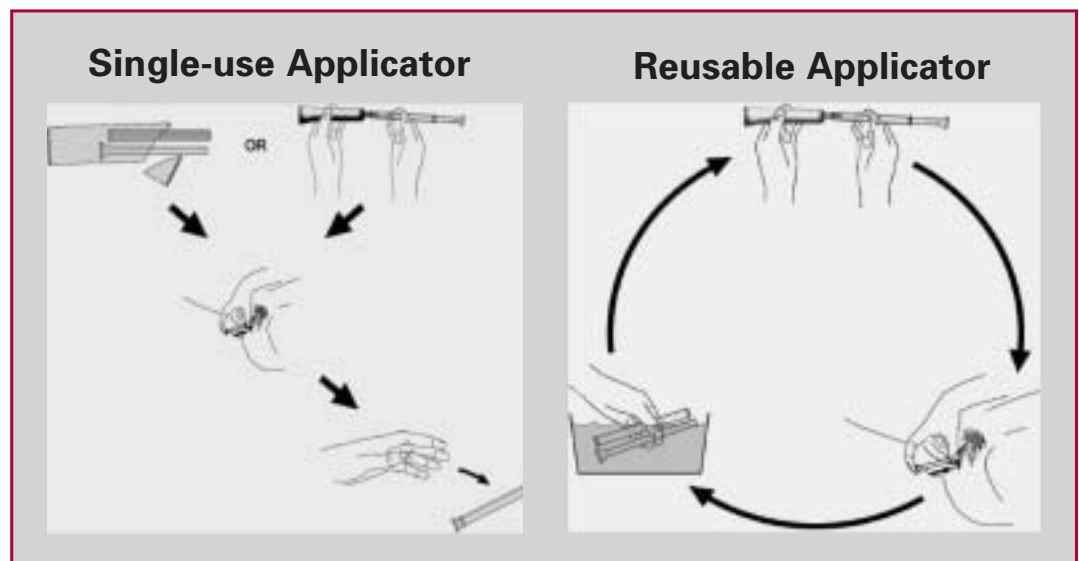
Many women say that microbicides would be unacceptable if they leaked, were messy, or required application just before sex (38). In a clinical trial of *BufferGel* in India, Malawi, Thailand, and Zimbabwe, some women reported that the formula was too wet, drippy, or sticky.

Since insufficient vaginal lubrication during sex is a common problem, microbicides could

improve sexual intercourse for women and men (1, 125). In the *BufferGel* study about half of the 100 women using the compound reported that their sexual pleasure was increased, and nearly as many reported that their partners' pleasure was increased (6).

To address people's diverse preferences, microbicide developers are likely to offer several different formulations, including

veys that are available, men appear to be interested in microbicides. In a 1999 survey of 243 South African men, over 75% said they would like their partners to use a microbicide, and most said they wanted to be involved in making the decision. Most respondents preferred a microbicide formulation that prevents STIs but does not also prevent pregnancy (98).



Researchers in the Dominican Republic and South Africa use illustrated charts to assess people's preferences for single-use or reusable applicators.

gels, films, creams, suppositories, foams, and sponges (51). Researchers also are exploring several different types of applicators, including reusable and prefilled applicators, single-use applicators, and vaginal rings (16, 117).

What do men say about microbicides? Most clinical trials and acceptability studies focus on women's views of microbicides (67). If microbicides are to be widely used, however, they should be acceptable to men as well (125). Based on the sur-

In focus-group discussions in Mexico, Zimbabwe, and the US in 1996–97, most of 106 men interviewed thought that microbicides would be preferable to condoms for preventing STIs, although they expressed concern about potential side effects. Some of the men thought that a woman should have permission from her partner before using a microbicide (15).

In South Africa in interviews and focus-group discussions, men said they were concerned that microbicide use would make

it difficult to distinguish whether a woman was wet due to the microbicide or because she had sex previously with another man. This study also found that women would be concerned about being accused of infidelity, having an STI, or having poor hygiene (22). For these reasons, women in the South African study, as well as other studies, report that they would want to tell their partners if they were using a microbicide (15, 34).

The few studies that have examined acceptability of micro-

bicides among men who have sex with men suggest that microbicides also are likely to prove acceptable for use in anal sex, particularly since using lubrication is popular among men whether or not they use condoms. In one study of 307 men who have sex with men, 92% said that they would use a lubricant with a microbicide (14).

Anal intercourse is a primary means of HIV transmission among both opposite-sex and same-sex couples (12, 36), and thus acceptability studies of

microbicide use during anal sex would be useful (67). Some microbicide advocates, however, call for deferring spending to test the effectiveness of a product for rectal use until it first proves safe and effective for vaginal application. If a product is not safe and effective as a vaginal microbicide, it also would not be appropriate for use rectally, and resources are too limited to spend on rectal safety and effectiveness studies before effectiveness for vaginal use has been demonstrated (108).

Ensuring Access Is Essential

If microbicides are to fulfill their promise, they must be accessible and affordable as well as safe and effective. A successful introduction strategy will involve manufacturers, suppliers, public health systems, and governments and will include communication, marketing, logistics, and pricing plans as part of the strategy. Strategies for promoting access and affordability—for example, advocacy to ensure that microbicides are included in Essential Drugs Lists—will be a key responsibility for the public sector (94).

How a microbicide is positioned in the marketplace could make the difference between limited acceptance and widespread use (1). Marketing strategies that introduce microbicides as a product for good reproductive health and healthy vaginal conditions, as a contraceptive (that is, if it is also spermicidal), or even as a product to enhance sexual pleasure could

promote widespread public acceptance. In contrast, initial promotion efforts aimed at sex workers or other high-risk groups could stigmatize microbicides among the general public and lead most people to reject them (1).

Because the first microbicides are likely to be less effective than male condoms, they should be promoted as an adjunct or back-up to condoms, rather than as a replacement, and for added pleasure (due to lubrication) and protection (49). Additionally, use of a microbicide along with a condom, diaphragm, cervical cap, or another barrier method probably would improve effectiveness against STIs. HIV, gonorrhea, chlamydial infection, and HPV transmission occur frequently in the cervix. Therefore, many researchers believe that contraceptive barrier methods such as diaphragms or cervical caps, which protect the cervix, offer STI protection (82),

although epidemiologic evidence has yet to establish this effect (45) (see **Population Reports**, *New Choices in Contraception*, forthcoming).

Community outreach and counseling. In areas where phase III clinical trials are planned, health care and civic organizations have begun introducing the concept of microbicides through community preparedness campaigns. For example, the Gender AIDS Forum, a South African nongovernmental organization (NGO), has developed and tested materials that explain microbicides in the English and Zulu languages. The materials are designed to make people aware of microbicides and to encourage their widespread use (115). In India a network of NGOs has begun to reach out to social workers, doctors, health counselors, and journalists about the potential of microbicides to empower women (8).



Community preparedness activities where clinical trials are not being conducted, and thus where there is little awareness of microbicides, also could help set the stage for successful introduction of microbicides.

Health care providers will be influential in how clients perceive microbicides (67). Counselors will need training to promote and provide microbicides without bias and in a nonjudgmental way to anyone who wants them. They also need to understand and be able to explain to individual users that microbicides are only partially effective in preventing STIs (22).

For people at risk of HIV and other STIs, counseling messages could advise using a condom every time they have sex. If they cannot use a condom, they should use a microbicide. Providers also could ask women to consider whether their partners will discontinue condom use if they begin to use microbicides (125). Providers should help clients to understand the relatively lower effectiveness against HIV of microbicides compared with consistent and correct use of condoms and encourage consistent and correct condom users to continue using condoms instead of switching to microbicides (22, 28, 106).

How would people obtain microbicides? To help ensure access, microbicides should not

require a doctor's prescription and should be available through a broad range of outlets, including pharmacies, health clinics, family planning clinics, community health workers, shops, taxi stands, markets, convenience stores, bars, and workplace dispensaries (1, 22). Community-based organizations also will have an important role in distributing microbicides to the groups they serve (1, 22, 94).

When health providers offer microbicides, they also can offer education, counseling, and support, which will be especially useful with their introduction. Also, preparing for the addition of microbicides to national supply chain systems will help ensure that they reach rural areas as well as urban areas. Planning for distribution needs to take account of the specific characteristics of each microbicide such as storage requirements, shelf life, and biostability—the ability of a microbicide product to maintain its physical and chemical integrity (1).

Will microbicides be affordable? Where the need for microbicides is greatest, they will require subsidization by international donor agencies and national governments (22, 81). According to one estimate, buying, distributing, and marketing microbicides to 10% of urban women in 66 low- and middle-income countries would cost almost US\$2 billion per year (62). This figure is based on the assumption that microbicides would cost US\$1 per application, including shipping, storage, and transportation—a cost unaffordable for many people in developing countries. Some microbicide

developers consider this unit cost to be an overestimate. CONRAD is aiming for a cost that is substantially lower—ideally, 10 US cents per application or less (30).

Many women, however, say they would be willing to pay a high price for the ideal microbicide. In the 1996–97 Brazil study, for example, almost half of the 635 women surveyed were willing to pay up to US\$5 per application (41). Similarly, a 1998 study among 4,000 urban women in 11 countries found that women would be willing to pay several times the price of a condom for a microbicide (52).

The total cost of offering microbicides in specific countries will reflect not only the production costs of the product itself but also the costs of registration, shipping, tariffs, duties, taxes, logistics systems, marketing, and similar expenses. Packaging and applicators are likely to account for a substantial proportion of the total cost (1).

The price of microbicides to consumers can be kept down. Governments could provide production incentives, including low-interest loans for building manufacturing plants. Reproductive health organizations and governments could buy microbicides and applicators in bulk and build on existing distribution systems for delivering microbicide products to users (1). If international donors and governments work together to devise finance strategies, microbicides could be accessible and affordable to all who want them (22).

Key Organizations Supporting Microbicide Development

Many organizations have provided substantial support for microbicide development. Some have given large grants to fund research. Others are conducting clinical trials. Still others are working to create public awareness of microbicides and help ensure that their introduction to the market will succeed.

The organizations listed below can provide further information about microbicides. Information also can be obtained from the biweekly e-mailed newsletter *GC News*, an international forum for exchange of information on microbicide development and other prevention options against STIs, including HIV/AIDS. To subscribe to the *GC News*, contact Global Campaign News, at <http://www.globalcampaign.org/signupGCNews.htm>.

Non-Profit Research Organizations

Family Health International (FHI), PO Box 13950, Research Triangle Park, NC 27709, USA, Telephone: +1-919-544-7040, Fax: +1-919-544-7261, E-mail: aidspubs@fhi.org or publications@fhi.org or services@fhi.org, Web site: www.fhi.org

Global Microbicide Project (GMP), CONRAD, Eastern Virginia Medical School, 1611 North Kent Street, Suite 806, Arlington, VA 22209, USA, Telephone: +1-703-524-4744, Fax: +1-703-524-4770, E-mail: info@conrad.org, Web site: www.gmp.org

HIV Prevention Trials Network (HPTN), E-mail: hptn@fhi.org, Web site: www.hptn.org

International Partnership for Microbicides (IPM), 1010 Wayne Avenue, Suite 1450, Silver Spring, MD 20910, USA, Telephone: +1-301-608-2221, Fax: +1-301-608-2241, E-mail: mmethot@ipm-microbicides.org, Web site: www.ipm-microbicides.org

Medical Research Council (MRC), Clinical Trials Unit, 20 Park Crescent, London W1B 1AL, UK, Telephone: +44 (0) 20 7670 4896, Fax: +44 (0) 20 7436 6179, E-mail: j.pickering@ctu.mrc.ac.uk, Web site: www.mrc.ac.uk/

Microbicide Development Project (MDP), Imperial College London, Clinical Trials Centre, Norfolk Place, London W2 1PG, UK, Telephone: +44 (0) 20 7886 6787 or +44 (0) 20 7670 4702, Fax: +44 (0) 20 7886 6123 or +44 (0) 20 767 4815, E-mail: l.colquhoun@imperial.ac.uk, Web site: www.mdp.mrc.ac.uk

Population Council, Center for Biomedical Research, One Dag Hammarskjold Plaza, New York, NY 10017, USA, Telephone: +1-212-327-7003, Fax: +1-212-755-6052, E-mail: microbicide@popcouncil.org, Web site: www.popcouncil.org

Prince Leopold Institute of Tropical Medicine (ITM), STD/HIV Research and Intervention Unit, Nationalestraat 155, B-2000 Antwerp, Belgium, Telephone: +32 (0) 3 247 6296, Fax: +32 (0) 3 247 6532, E-mail: vjespers@itg.be, Web site: <http://www.itg.be>

Program for Appropriate Technology in Health (PATH), 1455 NW Leary Way, Seattle, WA 98107-5136, USA, Telephone: +1-206-285-3500, Fax: +1-206-285-6619, E-mail: jvail@path.org, Web site: www.path.org

World Health Organization (WHO), Department of Reproductive Health and Research, 1211 Geneva 27, Switzerland, Telephone: +41 22 791 3641, Fax: +41 22 791 4189, E-mail: malonzai@who.int, Web site: www.who.int/reproductive-health

Major Donor Organizations

American Foundation for AIDS Research (amFAR), 120 Wall Street, 13th Floor, New York, NY 10005-3908, USA, Telephone: +1-212-806-1600 or +1-800-39-amFAR, Fax: +1-212-806-1601, E-mail: rowena.johnston@amfar.org, Web site: www.amfar.org

Bill and Melinda Gates Foundation, PO Box 23350, Seattle, WA 98102, USA, Telephone: +1-206-709-3100, Fax: +1-206-709-3180, E-mail: info@gatesfoundation.org, Web site: www.gatesfoundation.org/

Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, MS E-45, Atlanta, GA 30333, USA, Telephone: +1-404-639-6124, E-mail: lap5@cdc.gov, Web site: www.cdc.gov

Department for International Development (DFID), Policy Division, HIV/AIDS Team, 1 Palace Street, London SW1E 5HE, UK, Telephone: +44 (0) 20 7023 0824, Fax: +44 (0) 13 5584 3632, E-mail: r-gorna@dfid.gov.uk, Web site: www.dfid.gov.uk

European Union (EU), EC Programme for Action on Communicable Diseases, Fax: +1-212-688-1013, E-mail: delegation-new-york-euinfo@cec.eu.int, Web site: europa.eu.int

National Institute of Allergy and Infectious Disease (NIAID), Division of AIDS, 6700B Rockledge Drive, Bethesda, MD 20892-7628, USA, Telephone: +1-301-

496-8199, E-mail: rblack@niaid.nih.gov or cdeal@niaid.nih.gov, Web site: www.niaid.nih.gov

National Institute of Child Health and Human Development (NICHD), 6100 Executive Blvd, Room 8B13D, Rockville, MD 20852, USA, Telephone: +1-301-435-6991, Fax: +1-301-480-1972, E-mail: reichelp@exchange.nih.gov, Web site: www.nichd.nih.gov

Office of AIDS Research (OAR), Office of the Director, National Institute of Health, DHHS Bethesda, MD 20892, USA, Telephone: +1-301-496-3677, Fax: +1-301-496-4843, E-mail: fv10x@nih.gov, Web site: www.nih.gov/od/oar

Rockefeller Foundation, 420 Fifth Avenue, New York, NY 10018, USA, Telephone: +1-212-852-8321, E-mail: health@rockfound.org, Web site: www.rockfound.org

United Nations Population Fund (UNFPA), Reproductive Health Branch, 220 East 42nd St, New York, NY 10017, USA, Telephone: +1-212-297-5241, Fax: +1-212-297-5145, E-mail: edouard@unfpa.org, Web site: www.unfpa.org

United States Agency for International Development (USAID), Office of Population and Reproductive Health, Bureau for Global Health, 1300 Pennsylvania Avenue NW, Washington, DC 20523-3601, USA, Telephone: +1-202-712-0334, Fax: +1-202-216-3404, E-mail: lclaypool@usaid.gov or jspieler@usaid.gov, Web site: www.usaid.gov

World Bank, Global HIV/AIDS Unit, 1818 H Street, NW, Washington, DC 20433, USA, Telephone: +1-202-473-7856 or +1-202-473-9414, Fax: +1-202-477-6391, E-mail: jmacneil@worldbank.org or dzewdie@worldbank.org, Web site: <http://www.worldbank.org/aids>

Advocacy and Policy Research Organizations

Alliance for Microbicide Development, 8484 Georgia Avenue, Suite 940, Silver Spring, MD 20910, USA, Telephone: +1-301-587-9690, Fax: +1-301-588-8390, E-mail: pharrison@microbicide.org or cfox@microbicide.org, Web site: www.microbicide.org

Global Campaign for Microbicides, c/o PATH, 1800 K Street NW, Washington, DC 20006, USA, Telephone: +1-202-822-0033, Fax: +1-202-457-1466, E-mail: info@global-campaign.org, Web site: www.global-campaign.org



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